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(54) Title: IMMUNOGENIC PEPTIDE CARRIER CONJUGATES AND METHODS OF PRODUCING SAME

(57) Abstract: The present invention is directed to methods of producing conjugates of peptide immunogens with protein/polypeptide carrier molecules, which are useful as immunogens, wherein peptide immunogens are conjugated to protein carriers via activated functional groups on amino acid residues of the carrier or of the optionally attached linker molecule, and wherein any unconjugated reactive functional groups on amino acid residues are inactivated via capping, thus retaining the immunological functionality of the carrier molecule, but reducing the propensity for undesirable reactions that could render the conjugate less safe or effective. Furthermore, the invention also relates to such immunogenic products and immunogenic compositions containing such immunogenic products made by such methods.

WO 2005/058940 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/42701

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61K 39/00(2006.01),39/38(2006.01) USPC: 424/184.1,194.1,197.11,193.1,203.1,234.1,250.1 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/184.1, 194.1, 197.11, 193.1, 203.1, 234.1, 250.1 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 6645503 B1 (ARUMUGHAM et al.) 11 November 2003 (11.11.2003), entire patent.	1-2, 21-23, 55-68, 70-73, 75-76, 95-97, 129-143 and 145-148 2, 69-70, 74, 76, 144-145, 149
X — Y	US 5623057 (MARBURG et al) 22 April 1997 (22 04 1997), see entire patent.	1-2, 21-23, 55-69, 71-73, 75-76, 95-97, 129-144 and 146-148 2, 69-70, 74, 76, 144-145 and 149
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 22 March 2006 (22.03.2006)		Date of mailing of the international search report 04 AUG 2006
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201		Authorized officer Emily Le Telephone No. (571) 272-1600

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/42701

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y — A	US 5126131 (DINTZIS et al.) 30 June 1992 (30 06 1992), see claim 6.	2, 76 1, 3-20, 24-25, 30-44, 47-52, 77-9, 98-99, 104-118, 121-126, 150-151, 170-172, 204-205, 224-226, 262-263, 282-284, 314, 316-317, 336- 338.
Y — A	US 5877220 (SCHWARTZ et al.) 02 March 1999 (02 03 1999), see lines 20-30 of column 9.	74, 149 1, 3-20, 24-25, 30-44, 47-52, 77-9, 98-99, 104-118, 121-126, 150-151, 170-172, 204-205, 224-226, 262-263, 282-284, 314, 316-317, 336- 338.
A	US 5623057 (MARBURG et al) 22 April 1997 (22 04 1997), see entire patent.	1, 3-20, 24-25, 30-44, 47-52, 77-9, 98-99, 104-118, 121-126, 150-151, 170-172, 204-205, 224-226, 262-263, 282-284, 314, 316-317, 336- 338.
A	US 6645503 B1 (ARUMUGHAM et al.) 11 November 2003 (11.11.2003), entire patent.	1, 3-20, 24-25, 30-44, 47-52, 77-9, 98-99, 104-118, 121-126, 150-151, 170-172, 204-205, 224-226, 262-263, 282-284, 314, 316-317, 336- 338.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/42701

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
 2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
 3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
 4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
- Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/42701

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1,2,21-23,55-76, 95-97 and 129-149, drawn to methods of making a peptide immunogen-protein/polypeptide carrier conjugate, wherein the peptide immunogen is streptococcus pneumoniae and the carrier is human serum albumin.

Group II, claim(s) 150-151, 170-172, 204-205, 224-226, 262-263, 282-284 and 314, drawn to a peptide immunogen-protein/polypeptide carrier conjugate made by the method of Group I.

Group III, claim(s) 316-317 and 336-338, drawn to a methods of use for the peptide immunogen-protein/polypeptide carrier conjugate of Group II.

Group IV, claim(s) 1-25, 30-44, 47-52, 55-99, 104-118, 121-126 and 129-149, drawn to methods of making a peptide immunogen-protein/polypeptide carrier conjugate, wherein the peptide immunogen is Staphylococcus aureus, Staphylococcus epidermidis, Neisseria meningitidis, Neisseria gonorrhoeae, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae, Listeria monocytogenes, Vibrio cholerae, Clostridium perfringens, Clostridium botulinum, Pseudomonas aeruginosa, Salmonella typhimurium, Borrelia burgdorferi, Shigella flexneri, Sigella boydii, Shigella dysenteriae, Alloiococcus otitidis, Group B streptococci, HIV, HSV, HPV, PIV, VSV, RSV, EBV, coronavirus, vaccinia virus, rotavirus, rabies virus, HCV, HBV, renal cell carcinoma antigen, breast carcinoma antigen, carcinoembryonic antigen, melanoma (MAGE) antigen, prostate cancer specific antigen OR A-beta polypeptide; and the carrier is keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, influenza hemagglutinin, PADRE polypeptide, malaria circumsporozoite protein, hepatitis surface antigen, heat shock protein 65, Mycobacterium tuberculosis, cholera toxin, cholera toxin mutants with reduced toxicity, diphtheria toxin, CRM protein that is cross reactive with diphtheria toxin, recombinant Streptococcal C5a peptidase, Streptococcus pyogenes ORF1224, Streptococcus pyogenes ORF1664, Streptococcus pyogenes ORF2452, Chlamydia pneumoniae ORF367, Chlamydia pneumoniae ORF T858, Tetanus Toxoid, HIV gp120 T1, components recognizing microbial surface adhesive matrix molecules (MSCRAMMS), IL-1, IL-2, gamma-interferon, IL-10, GM-CSF, MIP-1alpha, MIP 1beta, RANTES, cytokines OR chemokines.

Group V, claim(s) 150-174, 179-193, 196-201, 204-228, 233-247, 250-253, 256-286, 291-304, 307-311, and 314-315, drawn to a peptide immunogen-protein/polypeptide carrier conjugate made by the method of Group IV.

Group VI, claim(s) 316-340, 345-358 and 361-365 drawn to a methods of use for the peptide immunogen-protein/polypeptide carrier conjugate of Group V.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/42701

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Carrier: keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, influenza hemagglutinin, PADRE polypeptide, malaria circumsporozoite protein, hepatitis surface antigen, heat shock protein 65, *Mycobacterium tuberculosis*, cholera toxin, cholera toxin mutants with reduced toxicity, diphtheria toxin, CRM protein that is cross reactive with diphtheria toxin, recombinant Streptococcal C5a peptidase, *Streptococcus pyogenes* ORF1224, *Streptococcus pyogenes* ORF1664, *Streptococcus pyogenes* ORF2452, *Chlamydia pneumoniae* ORF367, *Chlamydia pneumoniae* ORF T858, Tetanus Toxoid, HIV gp120 T1, components recognizing microbial surface adhesive matrix molecules (MSCRAMMS), IL-1, IL-2, gamma-interferon, IL-10, GM-CSF, MIP-1alpha, MIP 1beta, RANTES, cytokines and chemokines.

The claims are deemed to correspond to the species listed above in the following manner: 2-20, 76-94, 151-169, 201-223, 263-281 and 317-335.

The following claim(s) are generic: 1, 75, 150, 204, 262 and 316.

Peptide immunogen: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Vibrio cholerae*, *Clostridium perfringens*, *Clostridium botulinum*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Borrelia burgdorferi*, *Singella flexneri*, *Sigella boydii*, *Shigella dysenteriae*, *Alloiococcus otitidis*, Group B streptococci, HIV, HSV, HPV, PIV, VSV, RSV, EBV, coronavirus, vaccinia virus, rotavirus, rabies virus, HCV, HBV, renal cell carcinoma antigen, breast carcinoma antigen, carcinoembryonic antigen, melanoma (MAGE) antigen, prostate cancer specific antigen and A-beta peptide immunogen.

The claims are deemed to correspond to the species listed above in the following manner: 21-25, 30-34, 95-99, 104-109, 170-175, 179-183, 224-228, 233-235, 282-286, 291-295, 336-340 and 345-352.

The following claim(s) are generic: 1, 75, 150, 204, 262 and 316.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each of the listed species are structurally distinct from one another. The species do not share significant structural similarity with one another. In the absence of a significant structural similarity with each other, the species lack the same or corresponding special technical feature.

The inventions listed as Groups I-VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature shared among Groups I-VI is the peptide immunogen-protein/polypeptide carrier conjugate. It is found that the shared technical feature among the inventions does not contribute over the prior art. The prior art teaches of peptide immunogen-protein/polypeptide carrier conjugate, as evidenced by Arumugham et al., U.S. Patent No. 6645503. Arumugham et al. teaches a peptide immunogen-protein/polypeptide carrier conjugate, see abstract. Thus, Arumugham et al. demonstrates that the technical feature shared among the inventions does not provide a contribution over the prior art. In the absence of such, the technical feature shared is not a special technical feature. In the absence of a corresponding special technical feature, the inventions lack unity with one another.

Claims 26-29, 45-46, 53-54, 100-103, 119-120, 127-128, 175-178, 194-195, 202-203, 229-232, 248-249, 254-255, 287-290, 305-306, 312-313, 341-344, 359-360 and 366-367 are unsearchable for the following reason(s):

Claims 45-46, 53-54, 119-120, 127-127, 194-195, 202-203, 248-249, 254-255, 305-306, 312-313 and 359-360: These claims are unsearchable because it is unclear which A-beta peptide immunogen the claims are limiting.

Claims 26-29, 100-103, 175-178, 229-232, 282-290 and 341-344 fail to further limit its parent claims. These claims are directed at fungal and parasitic antigens, however, the scope of their immediate parent claim does not encompass these antigens. Claims 366-367 refer to the composition of claim 262 as a method. This is improper antecedent basis for claim 262.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/42701

Continuation of B. FIELDS SEARCHED Item 3:

EAST: PreGrant Pub, USPat, Derwent, EPO, JPO

search terms: albumin, streptococcus pneumoniae, peptide, conjugate, linker, method., immunogen, carrier.